Statement of

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Before the

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U.S. HOUSE OF REPRESENTATIVES

On the subject of

FDA's Foreign Drug Inspection Program

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A. Introduction:

Mr. Chairman, members of the Subcommittee on Oversight and Investigations, I thank you for this opportunity to discuss the status of FDA's oversight of the foreign-based pharmaceutical manufacturing industry and related drug products. I retired from FDA in February 2005 after 32 years of government service, 28 of which I served in the U.S. Food and Drug Administration, Office of Regulatory Affairs (ORA). Besides serving as a senior special agent with FDA's ORA/Office of Criminal Investigations, I served in capacities as a consumer safety officer carrying out duties as a field investigator, a resident-in-charge, a field compliance officer, a first line supervisor of a field unit dedicated to import operations, lead compliance officer with the original Team Biologics Core Team based in ORA headquarters, and, finally, for nearly six years, I served as Director of ORA's Division of Import Operations and Policy (DIOP). Since

my retirement I have been self-employed as a regulatory consultant and am founder and owner of C. Nielsen Consulting, an FDA regulatory consulting business.

B. Foreign Inspections and Drug Safety:

The inspection or audit of foreign manufacturers of components (including active pharmaceutical ingredients) and finished drugs is a critical activity to ensure the drug industry has implemented appropriate manufacturing steps and controls to ensure each batch of drug meets all product specifications and is safe. Basically, the facility inspection process verifies the facilities and equipment are adequate in design and construction, and verifies the manufacturing processes, and the quality control and testing procedures are in place and executed for each batch of drug product. FDA uses the designation "state of control" to characterize a firm that has implemented and adhered to good manufacturing practices that best ensures drug safety and effectiveness. The best manufacturing practices may include the testing of in-process materials, testing of air handling systems, testing of equipment performance, testing of cleaning operations between batches of production, testing of water systems, and the testing and monitoring of a myriad of other potential variables that, if left uncontrolled, could result in contaminated finished drug product or otherwise render the finished drug product unsafe or ineffective. There is not a battery of finished product testing that can replace good manufacturing practices to ensure the product safety and effectiveness for each dose of drug. If one just relied on finished product testing for product safety and effectiveness without regard to a controlled manufacturing process, then each tablet, pill, capsule, or vial would have to be tested to provide a 100% assurance the products are safe and

effective. Obviously, it would not make sense to destroy the entire production just for testing purposes.

The credible presence of an FDA inspection process can help provide some additional incentive for foreign industry to implement all the best practices to ensure the delivery of a safe and effective drug supply in the global marketplace. Certainly a foreign firm that knows there is a strong likelihood of being subjected to routine FDA inspections or equivalent will have greater incentive to have the manufacturing house in order for FDA product safety requirements. However, the current level and frequency of FDA foreign inspections is woefully wanting, regardless if the number of foreign prescription drug manufacturers to be inspected is 3,000 or 6,800 or many more.

The effectiveness of inspections is not just a matter of how frequently a firm is inspected, but also the quality and depth of inspection which is dictated, in part, by the inspector's expertise, available funds, and the time allowed by management for conducting the inspection. Foreign inspections are generally much shorter in duration compared to inspections of drug firms in the United States. The February, 2008 FDA inspection of Changzou SPL Company, Ltd., Changzou City, Jiangsu Province, China, conducted as a follow-up to the recent Heparin problems was five (5) days in duration according to the FDA-483, Inspectional Observations, posted on FDA's web site. It would be reasonable to expect an inspection of greater depth of at least twice as long or 10 days would have occurred if the subject plant and supply chains had been located in the United States rather than China.

C. FDA's Foreign and Domestic Inspection Program + Funding:

The FDA's Office of Regulatory Affairs (ORA) conducts the foreign inspections. There may be inspection team members from other FDA components, but generally ORA has the responsibility for accomplishing "X" number of foreign drug inspections per year as identified in the ORA Workplan. Inspection guidance is provided to the inspectors through a variety of documents. As an example, guidance for conducting domestic/foreign drug manufacturing inspections is primarily given through the Compliance Program Guidance Manual (CPGM) # 7356.002, entitled "Drug Manufacturing Inspections". Many of the programs are posted on the FDA web site under the "Manuals" link, including the cited program. The CPGM's articulate the rationale and strategies to be used by the inspectors for evaluating a firm's compliance with FDA requirements.

ORA is not directly funded for inspections and other post-market activities and must negotiate with the Center for Drug Evaluation & Research (CDER) through a work plan process to determine how many foreign inspections can be funded for the year. Generally, resources are allocated in the form of a Full-time Equivalent (FTE) by program for the year. The ORA work plan identifies the number of FTE's allocated to specific programs and related activities. The FTE is largely a time management tool. Less than 1 FTE may be allocated for a particular activity for a particular product category. Reportable activities for which inspectors and laboratory analysts report time spent

include facility inspections, sample collections, sample analyses, investigations, product examinations and entry review for imported drugs.

FDA's budget process and method of allocating resources is very confusing. In my previous testimony before this Subcommittee on November 1, 2007, I referred to a statement by former FDA Deputy Commissioner for Policy William B. Schultz before the Permanent Subcommittee on Investigations of the Senate's Committee on Government Affairs on September 24, 1998. Mr. Schultz provided information relative to the meaning of a "supported FTE". He said 565 FTE's translates to 314 "operational" staff or 112 actual investigators and 202 bench analysts. Apparently 251 of the 565 FTE or 44% of the FTE is required to support 314 personnel who conduct inspections and analyze samples and actually report time into the accountability system for program management.

As this Subcommittee reviews budget needs and considers legislative remedies to improve FDA oversight of regulated industries, I strongly suggest the current FDA budget process, the FTE model and ORA work plan process be evaluated and modified as needed. If significant new resources are provided to the Agency and the current system for work planning and allocating resources is used for deploying or allocating the resources, a newly funded 565 FTE, could result only in 112 inspectors based on historical management practices. This scenario in part explains why I was never able to obtain a roster of field inspectors/investigators dedicated to import operations during my nearly 6 years as Director of ORA's Division of Import Operations and Policy. The

current program management practice emphasizes FTE that may not be directly related to the location of trained individuals available to perform specific tasks in a particular geographic area.

D. Post-market Activities & Information Technology:

FDA's Office of Regulatory Affairs (ORA) is the organization that manages and supports all field operations. Primary post-market activities conducted by ORA include domestic/foreign inspections of all regulated commodities and industries; laboratory analyses; receiving and following-up consumer/trade complaints; monitoring product recalls; conducting investigations, and conducting import operations at the ports of entry.

The FDA Science Board's Subcommittee on Science and Technology Report, "Science and Mission at Risk" identified many weaknesses with the existing FDA infrastructure without evaluating in detail the current status of ORA's Information Technology (IT) needs. Just as the Science Board identified the need for enhanced post-market data to better enable product Center oversight of product safety, ORA also needs post-market information in an integrated fashion for use in a risk management approach. Daily priorities for a variety of activities must be established quickly regardless of the ORA staff size and location. The Science Board or a similar third party source should thoroughly assess ORA's infrastructure and processes in order to develop a meaningful proposed budget that could translate into remarkable improvement of public health and safety. ORA represents a primary front-line force that interacts directly with the

consumers, industry, and other federal and state government agencies in the post-market environment.

A risk based approach by FDA for determining admissibility of imported goods and preventing entry without verification of compliance can not be effectuated without significant investment in an integrated IT capability. ORA must use information from each of the Agency product Centers, including CDER, in order to make risk based decisions at the border and to plan inspections and other activities in a manner to best mitigate the greatest potential risks to public health. The development of a comprehensive risk model for a specific product includes both pre-approval and post-market information, i.e., inherent risks + product experience. Information related to product stability, recalls, adverse event reports, consumer/trade complaints, compliance with good manufacturing practice regulations, epidemiological information, exogenous information, and other relevant factors can contribute to a workable risk-based regulatory approach to drug safety and effectiveness in the global market. But effectiveness of a robust risk based approach is contingent on the development of appropriate IT for executing the regulatory approach. FDA must stop relying on its paper driven systems and move away from the "call X person who knows" or "find the memo" model of information sharing.

E. <u>Solutions are not just more of the same</u>:

Although significant new resources are required, those resources should not just be thrown to the Agency with a hope of better things to come based on the size or amount of new resources. Radical changes are needed in the organizational structure, management and IT systems to significantly improve Agency operations. All relevant product and facility based information, including drug applications, held by the Agency needs to be stored electronically in a readily searchable form for specific purposes. Many old drug applications and drug master files are still in paper form, which means the information is not readily available for use by the ORA field force to determine admissibility of imported drug products. It is not uncommon that industry has to spend significant resources providing hard copies of supplements to drug applications to local field offices as evidence of compliance of shipments of drugs offered for import even though the regulated firms have followed the regulatory requirements and properly submitted supplements and received approval letters from CDER. Not only does the current state of the broken, outdated FDA IT infrastructure pose increased risks to FDA functions and public health, it also increases the cost of doing business for both FDA and industry.

An effective FDA of the future must have the IT capabilities to support an “account” based approach for all regulated and registered facilities. The “account” should be a single, verifiable, unique, firm identifier as an anchor to which all historical and relevant information held by FDA is linked. There should be an FDA IT capability to enter a firm name, address and/or registration number to obtain a profile based on an automated rapid search of related information such as the drug applications, drug master files, drug labeling, FDA inspection reports, FDA laboratory results, recall histories, adverse event

reports, compliance histories, and importations into the United States. The same or similar information could then readily be applied to risk-based decisions by the Center and ORA during the course of targeting scant resources towards products that pose the greatest potential threat to public health.

The drug facility registration and product listing information submitted to and stored by FDA needs to be verified at the time of submission, and there needs to be a grandfather verification process for drug firms already registered and listed. The establishment of such a gatekeeper role would improve data integrity so a reliable data set could be used in administrative processes related to the registration and product listing. Legislation should be considered to make the firm registration process similar to an FDA "license" or "permit" for importation. Congress should consider promulgating FDA authorities to grant, deny, suspend, revoke, and re-instate registration based on the compliance status with FDA requirements. Linking an affirmative compliance status with registration information could transform the current registration process into a meaningful risk based system. Additionally, the establishment of a single unique account identifier for registered firms could enhance the effectiveness of FDA's Import Alert system. Firm identifiers and FDA product codes are critical elements for effective selectivity criteria when targeting shipments for interdiction or for expediting entry.

FDA's ORA organizational structure has remained basically the same over the last three decades with most resources devoted to oversight of regulated industry within the United States. Volunteers are solicited from the domestic inspection force to conduct foreign

inspections with varying success. Resources allocated for foreign inspections and oversight of imported products is nominal compared to resources for overseeing the domestic drug industry. The FDA ORA infrastructure and management systems are largely controlled by career government officials with interest towards preserving traditional domestic based operations. The lack of direct funding for ORA further aggravates the current dysfunction in the arenas of foreign inspections, border operations and IT development. Therefore, the Agency should be encouraged, if not mandated, to establish an organization funded and empowered to specifically oversee foreign regulated industry, traditional border operations, and the FDA import community. Such an organization would be better positioned to evaluate and monitor the entire supply chains or product life cycle of foreign made products to better ensure the delivery of safe products to the U.S. markets.

The findings from a robust foreign inspection program supported by effective IT would provide relevant information for targeting higher risk goods for examination at the border or for expediting movement of compliant goods. Inspections of product and receiving processes at the importer level could also generate relevant information for risk based targeting at the borders, and provide relevant information in selecting foreign firms for inspection. The establishment of a directly funded FDA designated unit for covering foreign industry, border operations, and importers with line authority to inspectors on the ground in the United States and foreign posts would best ensure efficient and effective use of government resources.